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Bis-cyclic Crown Ethers Derived from Biphenyl. Influence of Conformation in Complexation of $Hg(SCN)_2$

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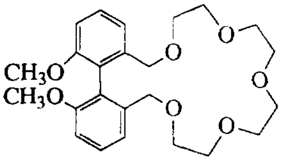
Abstract: Complexation studies carried out using bis-crown ethers derived from biphenyl have demostrated that the second crown units has a strong influence on the association constant in the first one. X-ray analysis shows that the situation is different in the monocrown-ether complex **5** than in the related bis-cyclic compound **6**.

Crown ethers containing biphenyl units in their structures have been widely studied because of the ability of the biphenyl system to transmitting conformational information or showing chiral barriers.[1,2] In our studies on macrocyclic compounds showing positive allosteric behaviour, biphenyl-19-crown-5 derivatives, **2** and **3**, have been synthesized.



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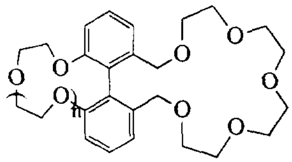
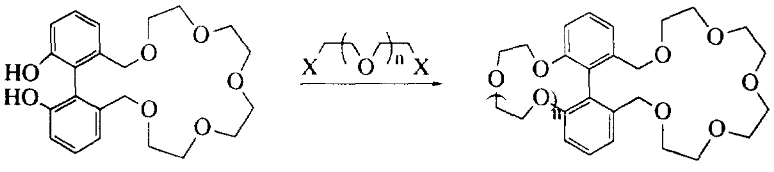


2 n=1
3 n=3

These compounds permitted us to study the influence of one of the crown ethers in the efficiency of the second crown donor atoms to be properly arranged to converge on the metal centre. In that sense, compound **1**[3] could be used as a model because it presents the same electronic characteristics but the methoxy groups should have a smaller influence on the crown ether conformation than a second ring bound to the 6,6' positions of the biphenyl unit.



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2 n=1
3 n=3

Compound **2** was synthesized from 6,6'-dihydroxy-biphenyl-19-crown-5 by a cyclization reaction with bis-(2-chloroethyl)ether. On the other hand, compound **3** was obtained from **4** by reacting it with tetraethylene glycol ditosylate.

DETERMINATION OF ASSOCIATION CONSTANTS

In order to know the influence of the second crown ether on the ability of the first one to complex metal ions, complexation studies with $Hg(SCN)_2$ were carried out. 1:1 complexes were prepared and studied by NMR; the use of this technique for the determination of association constants led to excellent results because a slow exchange occurred in the NMR experiments.

The association constants determined by NMR using acetone as a solvent are shown in Table 1. These data clearly indicated that the monocrown ether **1** complexes $Hg(SCN)_2$ better than the bis-crown ether derivatives. Taking into account that the three ligands are electronically similar, the different behaviour observed in **1** could be explained if a suitable arrangement of the donor atoms to complex the metal were easily adopted by the open crown than by the bicyclic compounds **2** and **3**.

Table 1. Association Constants ($Hg(SCN)_2$, acetone, 25°C)

Ligand	log K
1	3.43
2	2.15
3	1.92

On the other hand, experiments using different solvents have been carried out. Complex **2**· $Hg(SCN)_2$ shows a different behaviour when methanol and chloroform were used as solvents. In chloroform only the presence of the complex was observed in the NMR spectrum. In contrast, only the ligand was present in solution after dissolution of the complex in methanol. These facts suggest a preferentially enthalpy-driven complex formation. This behaviour was expected taking into account that the reaction was made from an uncharged ligand and a soft metal ion to give a mostly covalent complex.[4]

STRUCTURAL STUDIES

Complex **5**, obtained from **1** and $Hg(SCN)_2$ and complex **6**, prepared from **2** and $Hg(SCN)_2$ have been studied by X-ray analysis (figures 1 and 2). The structure of **5** had been previously described[5] and now we report the structure of **6** in order to make a comparative study between both structures.

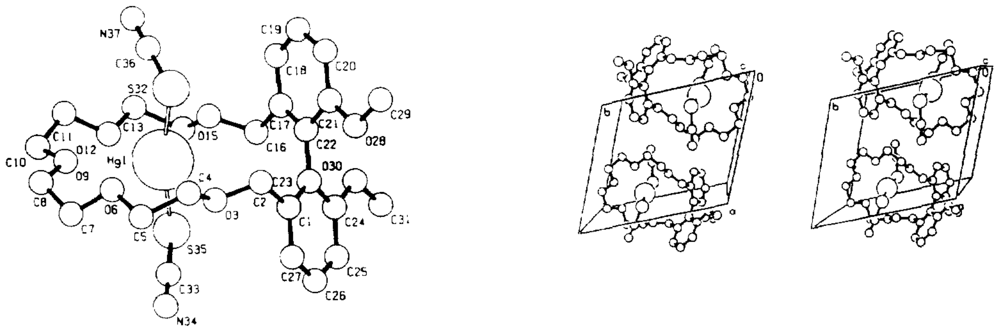

Figure 1. View of the molecular structure with crystallographic numbening scheme and a stereoscopic view of its crystal packing of complex **5**.

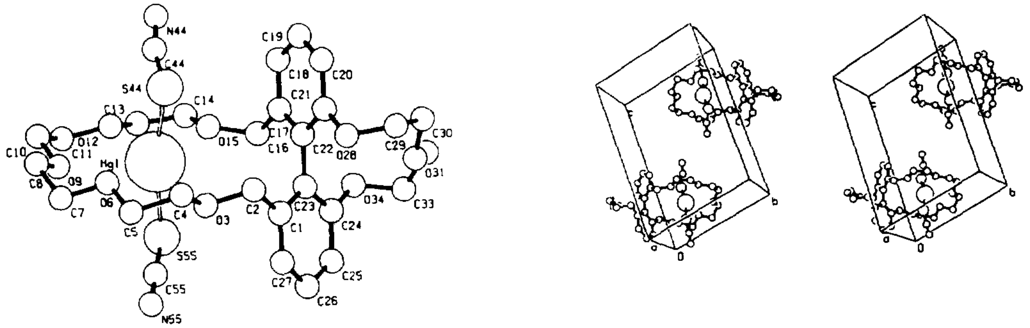

Figure 2. View of the molecular structure with crystallographic numbering scheme and a stereoscopic view of its crystal packing of complex **6**.

The comparison of these structures proves that in both complexes all the ethereal oxygen atoms participate in the coordination of mercury. In addition, in **5** and **6** the oxygen atoms in the ring are, on overage, 0.164 Å and 0.184 Å, respectively, from the oxygen mean plane and in neither ring do the oxygens alternate above and below this mean plane. In each complex the mercury atom is lying at approximately the oxygen mean plane and occuping a central position within the cavity. On the other hand, the Hg-S bond lengths are 2.374 Å in **5** and 2.362 Å in **6** which are according to the standard values.[6] The Hg-O coordination length means in **5** and **6** are unexceptional at 2.806 Å and 2.765 Å, respectively. Thus, in both complexes the Hg atom is coordinated equatorially by five oxygen atoms resulting in coordination polyhedra best described as distorted pentagonal bipyramidal.

However, clear differences are observed between both complexes. Thus, whereas complex **5** shows a very regular ring conformation with almost all C-O bonds antiperiplanar, a major departure from the macrocyclic ideallity appears in complex **6**. In complex **5** the C-C-O angles are close to tetrahedral, and the C-O-C angles are somewhat larger (Table 2). By contrast, complex **6** shows a pronounced asymmetry in the 5-oxygen cown ether moiety. In this sense, an opening of the C-C-O angles is observed from C(10) to O(15). As a consequence, the torsion angle about the C(14)-O(15) bond decreases from antiperiplanar to anticlinal conformation which is a difference with the cown-like shape associated with these macrocycles.[7] An additional asymmetry is observed in one of the SCN groups of **6**, which is placed above the asymmetric part of the crown ether. Thus, the angle S(44)-C(44)-N(44) is 165°, far from the expected value for a lineal group.

Table 2. Angles C-C-O and C-O-C for **5** and **6**.

Angle	Complex **5**	Complex **6**
C(1)-C(2)-O(3)	108.3 (6)	109.1 (7)
O(3)-C(4)-C(5)	108.7 (7)	109.6 (9)
C(4)-C(5)-O(6)	108.9 (6)	107.9 (9)
O(6)-C(7)-C(8)	110.7 (8)	108.6 (10)
C(7)-C(8)-O(9)	112.2 (8)	108.6 (10)
O(9)-C(10)-C(11)	111.4 (8)	111.5 (10)
C(10)-C(11)-O(12)	108.3 (8)	111.2 (10)
O(12)-C(13)-C(14)	108.6 (7)	115.8 (11)
C(13)-C(14)-O(15)	106.0 (6)	123.6 (12)
O(15)-C(16)-C(17)	107.2 (6)	110.5 (9)
C(2)-O(3)-C(4)	115.2 (6)	112.7 (7)
C(5)-O(6)-C(7)	113.8 (7)	111.5 (9)
C(8)-O(9)-C(10)	115.8 (8)	113.5 (9)
C(11)-O(12)-C(13)	112.6 (7)	116.4 (10)
C(14)-O(15)-C(16)	115.0 (6)	122.1 (11)

Surprisingly, the asymmetry observed in the 5-oxygen crown does not produce similar changes in the 3-oxygen ether moiety. A reason to explain this fact could be found in the small size of this crown which hinders any conformational distortion.

CONCLUSIONS

According to complexation experiments, the ability to form complexes with $Hg(SCN)_2$ decreases when a second crown ether is pesent in 6,6' positions of biphenyl system. One explanation for this behaviour could be found in the fact that the closing of the chain in the 6,6'posistions is expressed in a loss of freedom in the complexating crown to adopt a favourable conformation to complex the mercury salt.

As well as the data obtained in solution not being comparable to the X-ray informtion, differences between monocylic an bicyclic complexes are also observed in the solid state. Thus, complex **5** is more symmetrical than **6** which is according to the observed association constants. This loss of symmetry could be due to the presence of the second crown in the bicyclic compound.

EXPERIMENTAL SECTION

General methods

Compounds **1** and **4** were synthesized as described in the literature.[3] ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker AC-250, Varian Unity-300 and 400. Chemical shifts were reported from internal TMS. Mass spectra were taken on a VG AUTOSPEC mass spectrometer. TLC analysis were carried out on 0.2 mm Merck PC 60F245 silica gel plates. Column chromatographies were carried out on Merck 60 A-CC silica gel.

Synthesis of Macrobicycle 2

A dry 100-ml, three-necked flask was fitted with a reflux condenser, a thermometer, and an inlet pipe connected to a peristaltic pump. An inlet tube at the top of the reflux condenser was used to maintain a static argon atmosphere in the reaction vessel throughout the reaction. The flask was charged with **4** (0.4 g, $9.95\ 10^{-4}$ mol), and 12 ml of commercial 1-butanol before magnetic stirring was started, and NaOH in pellets (80 mg, $2\ 10^{-3}$ mol) was added. The mixture was heated rapidly to reflux (about 115°C), and a solution of bis(2-chloroethyl) ether in 10 ml of 1-butanol was added through a thin tube using a precision pump with continuous stirring and heating, as slowly as possible. After the resulting mixture had been refluxed with stirring for 24 hours, the hot mixture was filtered. By removing the solvent in a rotatory evaporator (15 mbar, 40°C), a semisolid compound was obtained. After silica gel chromatography (hexane/ethylacetate 1:3, rising polarity) compound **2**,108 mg (22.9%), was obtained as a white solid, m. p. 74-76°C. 250MHz ^1H NMR ($(CD_3)_2CO$) δ 7.72 (1H, t, J=7.9 Hz), 7.59 (1H, d, J=7.9 Hz), 7.41 (1H, d, J=7.9 Hz), 4.71 (1H, m), 4.66 (1H, d, J=11.8 Hz), 4.48 (1H, d, J=11.8 Hz), 4.43 (1H, m), 4.02-3.97 (10H, m). ^{13}C NMR ($(CD_3)_2CO$) δ 155.7 (s), 139.2 (s), 128.2 (d), 125.9 (s), 121.0 (d), 113.5 (d), 71.1 (t), 71.0 (t), 70.7 (t), 70.2 (t), 69.9 (t). Exact mass calcd 474.2253, found 474.2252.

Synthesis of Macrobicycle 3

6,6'-dihydroxy-2,2'-biphenyl-19-crown-5 (**4**), 400 mg ($9.95\ 10^{-4}$ mol), and NaOH, 80 mg ($2\ 10^{-3}$ mol), were dissolved in 12 ml of 1-butanol. The solution was stirred and heated under reflux for 1 day. Then, an additional portion of 1-butanol, 48 ml, was added. After the reflux temperature was again reached, a solution of tetraethylene glycol ditosylate ($9.95\ 10^{-4}$ mol) in 25 ml of 1-butanol was added through a thin tube using a precision pump with continuous stirring and heating, as slowly as possible, (4-5 h). The reaction mixture was refluxed, with stirring, for 24 h. After this time, the 1-butanol was removed in a rotary evaporator (15 mbar, 40°C) to obtain a suspension. Then, dichloromethane, 30 ml, was added and the solid obtained was separated by filtration. The organic phase was washed with aqueous NaOH (10%, 2x15 ml) and water (2x15 ml) and dried ($MgSO_4$). Removal of solvent by rotatory evaporation afforded an oil that was purified by silica gel column chromatoganphy (hexane/ethyl acetate 2:3, rising polarity) to give 115 mg (20.1%) of clear oil which solidified on standing. 250MHz ^1H NMR ($(CD_3)_2CO$) δ 7.74 (1H, t, J=7.9 Hz), 7.59 (1H, d, J=7.9 Hz), 7.45 (1H, d, J=7.9 Hz), 4.66-4.56 (2H, m), 4.43-4.33 (1H, m), 4.25-3.75 (15H, m). ^{13}C NMR ($(CD_3)_2CO$) δ 156.0 (s), 139.2 (s), 127.9 (d), 124.6 (s), 120.0 (d), 111.3 (d), 70.9 (t), 70.7 (t), 70.6 (t), 70.4 (t), 70.3 (t), 70.2 (t), 70.0 (t), 69.3 (t), 68.1 (t). Exact mass calcd. 562.2777, found 562.2778.

*Synthesis of **1**•$Hg(SCN)_2$ (5)*

To 1 equiv of **1** in acetone was added 1 equiv of $Hg(SCN)_2$ in acetone. After stirring for 1 minute the solution was kept at room temperature for 24 hours. After that time **1**•$Hg(SCN)_2$ was separated by filtration, m.p. 208 °C· Slow recrystallization from acetone afforded crystals suitable for X-ray analysis.

*Synthesis of **2**•$Hg(SCN)_2$ (6)*

To 1 equiv of **2** in acetone was added 1 equiv of $Hg(SCN)_2$ in acetone. The solution was stirred for 10 minutes and cooled to 4 °C. **6** was separated by filtration, m. p. 204-207 °C. The white solid was recrystallized from acetone to afford cystals suitable for X-ray.

*Synthesis of **3**•$Hg(SCN)_2$ (7).*

To 1 equiv of **3** in acetone was added 1 equiv of $Hg(SCN)_2$ in acetone. The solution was stirred for 4 hours and the solvent evaporated to give **7**, m. p. 152-154 °C. Suitable crystals for X-ray analysis could not be obtained.

Determination of Association Constants .

In an NMR tube 0.0015 mmol of the complex was dissolved in 0.9 ml of acetone-d_6. The reference standard (Me_4Si) was added, and the tube was capped with Teflon tape. The NMR spectra were recorded on a 400 MHz spectrometer at 298K. From the part of the spectra where different signals were observed for both species in solution (ligand and complex), a ratio R between free form and complex could be determined and from it K_a values could be obtained.

X-ray Structure Analysis.

Information concerning crystallographic data collection and refinement for complex **6** are summarized in Table 3. Intensity measurements were made on an Enraf-Nonius CAD4 diffractometer using a single crystal of dimensions 0.12 x 0.09 x 0.06 mm. Graphite-monochromated Mo-Kα radiation (λ=0.71069 Å) and ω-scan technique was used. Data collection was carried out at room temperature. Three reference reflections were measured every 2 hours as an intensity and orientation check and no significant fluctuation was noticed during the collection of the data. Lorentz-polarization and empirical absorption (Ψ scans) corrections were made. The crystal structure was solved by direct methods[8] using the MULTAN system and refined by full-matrix least-squares techniques[9] on F^2. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were constructed with the SHELXL93-Program with fixes isotropic displacement parameters. Fractional atomic coordinates with standard deviations (in parentheses) and equivalent isotropic temperature factors U(eq) are shown in Table 4.

Table 3. Crystallographic Data and Structure Refinement for Complex **6**.

Empirical formula	$C_{28}H_{34}HgN_2O_8S_2$
Formula weight	791.28
Temperature	293(2)K
Wavelength	0.71069 Å

Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.380(2)Å	alpha = 82.64(2)°
	b = 11.317(2)Å	beta = 89.12(2)°
	c = 16.246(2)Å	gamma = 86.84(2)°
Volume	1542.5(5)$Å^3$	
Z	2	
Density (calculated)	1.704 Mg/m^3	
Absorption coefficient	5.174 mm^{-1}	
F(000)	748	
Crystal size	0.12 x 0.09 x 0.06	
Theta range for data collection	1.25 to 29.96 deg.	
Index ranges	h = -11→ 11, k = -15→ 15, l = 0→ 23	
Reflections collected	9233	
Independent reflections	8944 [R(int) = 0,0218]	
Absorption correction	Semi-empirical from psi-scans	
Max. and min. transmission	0.733 and 0.537	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8942 / 0 / 370	
Goodness-of-fit on F^2	1.123	
Final R indices [I>2sigma (I)]	R(F) = 0.0897, wR(F^2) = 0.2194	
R indices (all data)	R(F) = 0.1051, wR(F^2) = 0.2356	
Largest diff. peak and hole	8.399 and -5.715 e.$Å^{-3}$	

The plots for the molecule and its packing in the unit cell have been made with PLUTON.[10] Geometrical calculations were performed by using PARST.[11] A list of anisotropic displacement parameters for non-hydrogen atoms, bond lengths and angles, torsion angles, hydrogen atom coordinates and tables of calculated and observed structure factors (F_o-F_c) have been deposited as supplementary material at the Cambridge Crystallographic Data Centre.

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for $C_{28}H_{34}HgN_2O_8S_2$. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Hg(1)	1471(1)	2668(1)	2033(1)	49(1)
S(55)	3163(5)	2490(5)	883(3)	102(1)
C(55)	2071(17)	2089(13)	211(8)	75(3)
N(55)	1362(27)	1793(19)	-312(10)	118(6)
S(44)	-17(8)	2468(5)	3269(3)	128(2)
C(44)	773(34)	3249(21)	3843(14)	125(7)
N(44)	1342(43)	3598(32)	4396(18)	219(14)
O(3)	84(7)	603(5)	1591(4)	52(1)
O(6)	-1485(9)	2933(6)	1333(4)	60(1)
O(9)	378(10)	4923(7)	1348(5)	74(2)
O(12)	3000(11)	4578(7)	2384(6)	73(2)
O(15)	4211(12)	2306(7)	2987(8)	98(4)
C(1)	2272(10)	-789(7)	1960(5)	51(2)
C(2)	563(11)	-427(8)	2140(6)	57(2)
C(4)	-1587(12)	830(10)	1575(8)	67(2)
C(5)	-1998(12)	1929(11)	984(8)	70(3)

C(7)	-1759(16)	3996(12)	800(8)	78(3)
C(8)	-1291(16)	5023(10)	1227(9)	83(3)
C(10)	950(16)	5844(9)	1734(9)	81(3)
C(11)	2619(19)	5679(10)	1875(10)	88(4)
C(13)	4622(15)	4357(10)	2620(12)	91(5)
C(14)	5004(20)	3245(13)	3048(16)	139(9)
C(16)	4893(13)	1139(9)	3187(8)	65(2)
C(17)	3757(12)	377(9)	3691(6)	59(2)
C(18)	3326(15)	621(11)	4480(7)	76(3)
C(19)	2300(18)	-91(15)	4966(6)	93(4)
C(20)	1685(16)	-1042(14)	4702(7)	85(4)
C(21)	2092(11)	-1325(9)	3930(6)	65(2)
C(22)	3099(10)	-614(7)	3405(5)	53(2)
C(23)	3470(9)	-917(6)	2568(5)	45(1)
C(24)	5005(9)	-1335(7)	2368(6)	52(2)
C(25)	5366(11)	-1556(10)	1560(7)	66(2)
C(26)	4236(13)	-1406(10)	978(6)	68(2)
C(27)	2675(12)	-1047(8)	1184(6)	61(2)
O(28)	1490(9)	-2286(7)	3620(5)	77(2)
C(29)	1812(20)	-3448(12)	4078(10)	94(4)
C(30)	3493(22)	-3617(12)	4394(10)	104(5)
O(31)	4522(13)	-3380(7)	3724(6)	80(2)
C(32)	6093(16)	-3183(12)	3927(8)	83(3)
C(33)	6913(13)	-2567(9)	3199(8)	73(3)
O(34)	6176(8)	-1400(5)	2948(5)	61(1)

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